REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended.

In the Advisory Action dated January 8, 2007, the Examiner suggests that the amendment to recite that methotrexate is administered intrathecally into the spinal cord but not the brain lacks basis in the original disclosure and is not explicitly recited in the instant specification. Applicants respectfully point out the basis for the amendment to the claim to recite "intrathecally into the spinal cord but not into the brain" is the knowledge of one of skill in the art at the time the application was filed. As discussed in the previous responses, support for this amendment can be found in the teachings of the general principles of human physiology and pharmacokinetics that intraventricular administration will not produce a local concentration of active drug in the spinal cord area that is anywhere near the same concentration as would be achieved with intrathecal administration. As discussed in the previous responses to Office Actions in this case, this is because, as taught in basic human anatomy and physiology texts (e.g., *Human Anatomy and Physiology*, Second Edition, Elaine N. Marieb (editor), Benjamin Cummings Publishing: Redwood City, CA, pages 404-405, starting at the second column on page 404, a copy

of which was provided with the response filed on May 11, 2006) the circulation of cerebrospinal fluid through the brain ventricles is designed such that only a very small amount of the cerebrospinal fluid from the ventricles circulates into the central canal of the spinal cord. As is taught in this text, "most enters the subarachnoid space" (see page 404, second column, line 3-4 of second paragraph). Therefore, intraventricular injection of methotrexate would result in only a small amount of circulation of the injected drug, via the cerebrospinal fluid, into the spinal cord. The drug instead would be considered as being injected into the brain when it is given intraventricularly. Further, following intraventricular injection, the concentration of methotrexate achieved would not be expected by one of skill in the art to be as high as could be achieved through direct administration into the spinal cord area via intrathecal administration. The subarachnoid space, as shown in Figure 12.20 on page 404 of the text cited above, is not the area touched through intrathecal administration. Most importantly, one of skill would understand that intraventricular administration leading to subdural circulation is referring to the subdural area of the brain NOT the spinal cord. This is again a basic anatomical feature that allows for separation of the brain and spinal cord areas in the body. Therefore, in

amending the language of claim 1, Applicants have relied on support found in the general principles of physiology and anatomy that were known at the time the application was filed. Applicants further point out that contrary to the Examiner's suggestion, Applicants are not relying on the concentration of methotrexate in CSF specifically but on the generally known fact that intrathecal administration leads to a higher dose in the spinal column than would intraventricular administration.

In the Advisory Action the Examiner has also suggested that the Chamberlain reference (a copy of which was provided with the response filed on September 21, 2004) cited as prior art under 35 U.S.C. 103(a) involves administration the same amount of methotrexate to a patient who has radiculopathy. The Examiner also is suggesting that this prior art reference teaches administration that would circulate into the spinal cord and that one of skill would use doses of methotrexate either as mg/m2 or in 1 to 2 mg doses, not based on body weight.

Applicants respectfully point out that the reference of Chamberlain is teaching treatment of leptomeningeal metastases with methotrexate. By definition, leptomeningeal metastases is cancer that has spread from the original tumor site to the tissues that cover the brain (http://www.cancer.gov/Templates /db_alpha.aspx?CdrID=45318, copy enclosed). Review of the paper

by Chamberlain reveals that what is being treated with methotrexate is the cancer, NOT radiculopathy as being claimed by the Examiner. Although 2 of the patients presented with radiculopathy, nowhere doe this paper teach or suggest that symptoms of radiculopathy specifically are reduced when methotrexate is administered. Instead, the only endpoints measured in the paper are endpoints relevant to the cancer itself, in particular improvement in CSF flow due to blockage by the tumor metastases. Therefore, the use of methotrexate is to shrink the size of the tumors. The methotrexate itself is NOT taught to affect any specific endpoint relevant to assessing efficacy to reduce lower back with radiculopathy as claimed in the instant claims.

In an earnest effort to advance the prosecution of this case, and as discussed in previous replies, Applicants have amended the language of claim 1 to recite that the method of the instant invention involves administration of a dose level of 1 mg/kg per dose, not to exceed a total dose of 2 mg/kg each day. Support for these amendments to the claims is found at pages 8 and 9 of the specification as filed. Applicants refer the Examiner to page 8, lines 14-33, for specific teaching of the dose range of between 1 and 3 mg methotrexate per kg of body weight (mg/kg). In that section it is stated that the dosage

"shown to be effective in these studies was low, 1 mg/kg." (see lines 14-15). Then, the section goes on to state that the dose administered to rats, 1 mg/kg, was one quarter of the maximally tolerated dose in rats (lines 22-25). That means to one of skill that a dose as high as 4 mg/kg would be contemplated since the maximum tolerated dose is known by one of skill to be the dose that one does not want to exceed in order to administer a drug or agent safely to an animal. Then at page 9, Example 1, line 28, it is taught that the total dose administered to the animals and shown to be effective was two doses of 1 mg/kg, total dose of 2 mg/kg. Therefore, the specification as filed clearly defines doses to be used as between 1 and 3 mg/kg. However, in an earnest effort to be very clear, Applicants have amended claim 1 to recite that the dose used is 1 mg/kg per injection up to a total dose of 2 mg/kg per day. This amendment to the claim is clearly supported by teaching of the specification as filed. Moreover, as the specification points out, the dose claimed is a "low dose" and as such it would not be expected that this dose would have the therapeutic efficacy shown in the specification as filed. The prior art literature fails to teach use of methotrexate as claimed for treatment of lower back pain with radiculopathy at the low doses claimed. Therefore, Applicants strongly disagree with the Examiner's

suggestion that the reference of Chamberlain et al. teaches use of a dose range that overlaps with that of the instant invention.

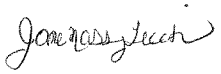
Chamberlain et al. disclose only use of a 2 mg dose of methotrexate, intraventricularly, in humans to treat a form of metastatic cancer. Nowhere in this reference is it suggested or taught that the 2 mg dose could be modified and given to any other species on the basis of mg drug per kg body weight. Although it is true that methotrexate is often dosed on a mg/m2 basis in cancer therapy, this is NOT the case for drugs used to treat pain. This is because, as taught in the specification as filed, one of skill would need to understand how efficacy related to safety in any particular species. That is why the teaching of the specification as filed is clear in defining dose on a mg/kg basis, to allow one of skill to understand how to extrapolate doses across different species. Chamberlain et al., however, is silent on this issue and thus would not be used by one of skill to extrapolate from a 2 mg dose in humans, which they would understand to be a dose of approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual, to a dose in a smaller animal such as a rat. The 2 mg dose of Chamberlain et al. is much lower than the dose range claimed in the instant invention and as such would

not be obvious to one of skill in the art. It must be remembered that it is a general principle of pharmacology to extrapolate doses across species based on mg/kg not mg alone and not on mg/m2 for pain treatment. Therefore, one of skill would automatically convert the 2 mg dose of Chamberlain to its mg/kg dose and then dose another species based on that dose. Using this procedure, one of skill would administer a 2 kg animal a dose of 2 x 0.033 or 2 x 0.029 mg/kg which would be a dose of from 0.058 to 0.066 mg NOT 2 mg as suggested by the Examiner in the Office Action. Based on use of standard practice in the art of pharmacology, there is no overlap between any of the teaching of Chamberlain et al. and any dose range claimed in the instant invention.

In order to establish a *prima facie* case of case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly the reference cited fails to teach or suggest the invention as claimed. The reference cited, in fact, teaches use of

methotrexate to treat cancer NOT lower back pain with radiculopathy. Second, the paper teaches use of a much lower dose range and a different route of administration. Therefore, this reference fails to teach the limitations of the claim as amended and also fails to provide one of skill with an expectation of success. It is only with the specification in hand that one of skill would understand that intrathecal administration at that particular dose level would be effective for treating lower back pain with radiculopathy. Accordingly, this reference cannot make obvious the invention of the amended claim.

Respectfully submitted,



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